Pulmonary hypertension

A rare but important cause of dyspnoea

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Pulmonary hypertension can be a devastating disease that is easily missed in the early stages because of its typically nonspecific presentation with gradually increasing dyspnoea. With advances in management, most forms of pulmonary hypertension are treatable. Early diagnosis and treatment are key to improving functional and haemodynamic outcomes and survival.

© BAYER. PULMONARY ARTERIAL HYPERTENSION

Pulmonary hypertension (PH) is a pathophysiological condition characterised by an increase in the mean pulmonary artery pressure. It is defined by a mean pulmonary artery pressure of 25 mmHg or higher at rest, measured during right-heart catheterisation. A change to this threshold, to a mean pulmonary artery pressure of more than 20 mmHg, was recently proposed.[1] If untreated, PH can be a devastating condition with high morbidity, and mortality rates that are poorer than for many metastatic malignancies. Increased recognition of patients with PH, allowing early diagnosis and intervention, is the focus of current management campaigns to alter the natural history of this disease.

Classification of pulmonary hypertension

Conditions that cause PH are classified by the WHO into five major groups based on shared pathophysiological mechanisms, which guide the therapeutic approach. The WHO diagnostic groups are:

- **Group 1** – also known as pulmonary arterial hypertension (PAH); this group comprises conditions where obstructive changes to the small pulmonary arteries leading to increased pulmonary vascular resistance are the primary abnormality
- **Group 2** – PH secondary to left heart disease
- **Group 3** – PH secondary to chronic lung disease or hypoxia
- **Group 4** – chronic thromboembolic PH, typically a sequela of unresolved pulmonary embolism
- **Group 5** – PH with unclear or multifactorial mechanisms.[2]

Conditions included in the five WHO diagnostic groups are listed in Box 1.[2] These

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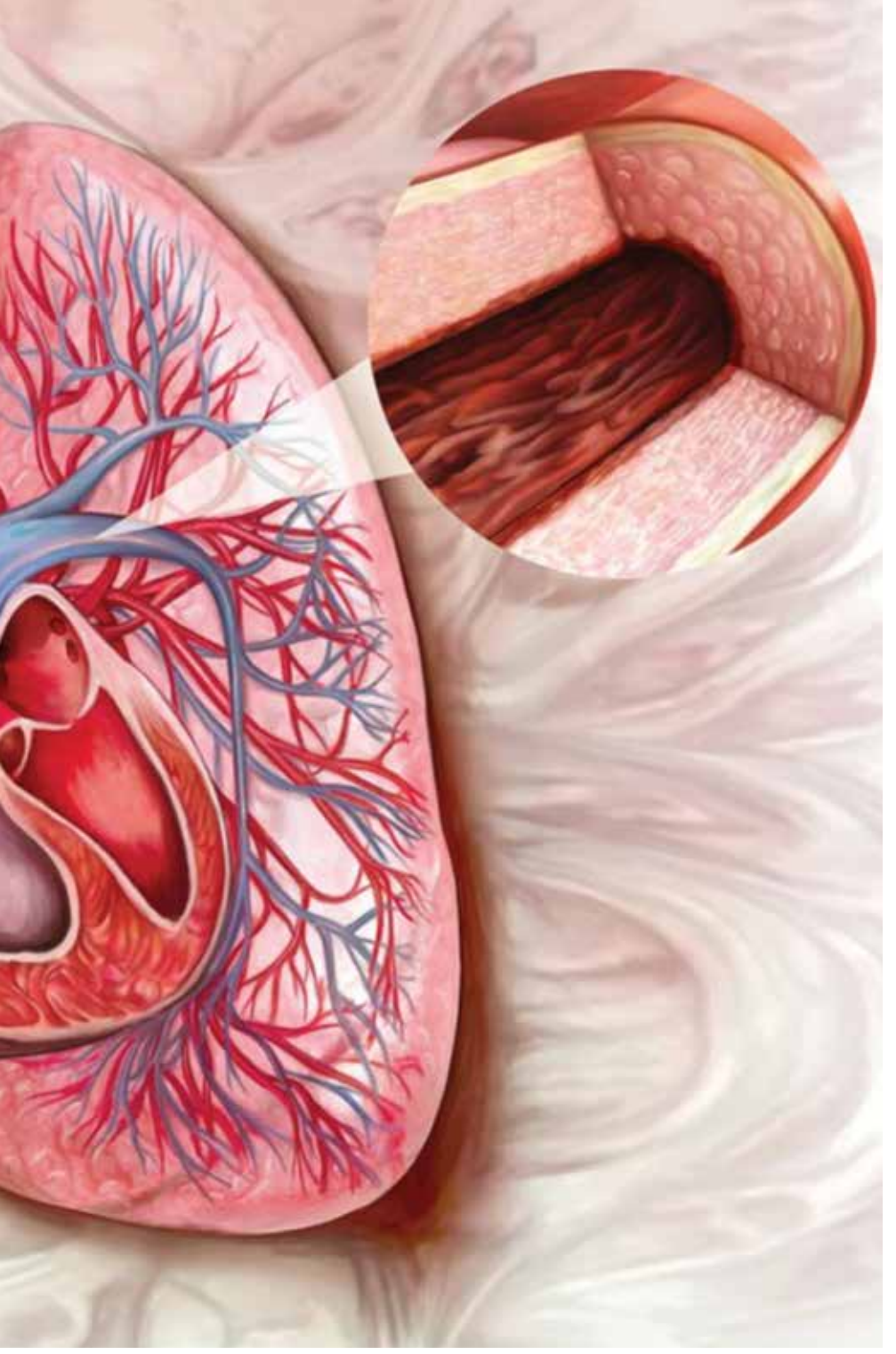


Key points

- **Pulmonary hypertension (PH) is characterised by an elevation in pulmonary artery pressure at rest and presents with progressive breathlessness as the cardinal symptom.**
- **PH can be associated with more than 50 different conditions, which are categorised into five groups based on pathophysiological mechanisms; accurate classification is crucial to management as treatment options and goals vary between groups.**
- **As symptoms of PH can be vague or nonspecific, diagnosis is often delayed, with patients typically progressing to advanced disease before diagnosis.**
- **Identifying patients early in the disease course can improve functional and haemodynamic outcomes.**
- **Group 1 PH (pulmonary arterial hypertension [PAH]) is rare; if it is suspected then prompt referral of the patient to a specialist with an expert interest in PH is recommended.**
- **Long-term management of patients with PAH, Group 4 (chronic thromboembolic) or Group 5 (unclear or multifactorial) PH should be delivered or co-ordinated through a designated PH clinic or service.**

WHO diagnostic groups are distinct from the WHO functional class system (Classes I to IV), which was adapted from the NYHA functional class system.

Accurate diagnosis of the PH group is crucial to ensuring management is targeted to the underlying pathophysiology. For example, selective pulmonary vasodilators are the only proven drug therapies for patients with PAH and Group 4 PH. However, their use to treat patients with PH in other groups may precipitate pulmonary oedema or other adverse cardiac events (Group 2 PH) or exacerbate hypoxia and breathlessness (Group 3 PH).

Group 1. Pulmonary arterial hypertension

PAH (Group 1 PH) is a progressive and often devastating condition. Proliferative changes in the lung microcirculation lead to increased pulmonary vascular resistance. If untreated, this results in right heart remodelling and ultimately right heart failure and death. Historically, patients with PAH had a grim prognosis, but in the past 15 to 20 years their functional status and life expectancy have improved significantly with major developments in targeted drug treatments.

Group 2. PH secondary to left heart disease

PH secondary to left heart disease (e.g. ventricular or valvular disease) is the most common type of PH. Treatment of the underlying disease and risk factor modification

1. WHO classification of pulmonary hypertension[2]

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.3 Drug and toxin induced
1.4 Associated with:
- 1.4.1 connective tissue disease
- 1.4.2 HIV infection
- 1.4.3 portal hypertension
- 1.4.4 congenital heart diseases
- 1.4.5 schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Other

3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed obstructive and restrictive patterns
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage and Gaucher disease, thyroid disorders
5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

are key to management. Stiffness of the left ventricle (heart failure with preserved ejection fraction) is increasingly identified as a cause of PH.

Group 3. PH secondary to lung disease or hypoxia

PH secondary to lung disease, sleep-disordered breathing or hypoxia is relatively common. Optimising the underlying condition with appropriate therapy, supplemental oxygen and respiratory support is the key to management. Typically, patients do not benefit from targeted drug treatment.

Group 4. Chronic thromboembolic PH

Chronic thromboembolic PH is thought to occur secondary to vascular remodelling of the pulmonary arteries in the setting of mechanical obstruction by unresolved thrombus. The underlying pathophysiology is similar to that of PAH. Where possible, surgical intervention with pulmonary endarterectomy is the preferred treatment, as it has the potential to 'cure' PH. However, interventional radiological approaches or targeted drug therapy can be used in patients deemed

2. Case history: a middle-aged woman with progressive dyspnoea

Case history

Amy is a 46-year-old executive assistant with progressively worsening dyspnoea on exertion. She used to enjoy sport and was always active. However, in the past few years, her breathlessness has worsened, and she has stopped playing sport and gained 10kg in weight (body mass index, 32kg/m^2). She was diagnosed with asthma in her early 20s and takes regular budesonide-formoterol and as-required salbutamol. Initially she found the inhalers of benefit but now she struggles to walk up the stairs at work. Her symptoms are attributed to lack of fitness, obesity and asthma.

Learning points

- Pulmonary arterial hypertension (PAH) is rare, with an estimated prevalence of 15 cases per million. Historically, it was reported to affect women aged in their mid-30s. Current registries show a female predominance but a mean age at diagnosis of 50 to 65 years.[3]
- Despite improvements in disease awareness, a long delay between onset of symptoms and diagnosis remains a barrier to initiating treatment. Registry data show delays in diagnosis of over 2 years, with 75% of patients presenting with severe symptoms.[4]
- A high index of suspicion for pulmonary hypertension (PH) is required as the typical presenting symptoms of dyspnoea, fatigue and exercise intolerance are nonspecific. PH should be suspected especially if the patient fails to respond to therapy for more common causes of breathlessness.
- Symptoms, exercise endurance and haemodynamics are important prognostic indicators in patients with PAH. Hence, identification of the condition at an early stage is crucial to improving patient outcomes.

Case history *continued*

During winter, Amy develops a flu-like illness and has a presyncopal episode. Her GP records an ECG, which is abnormal, and refers her to a cardiologist for further investigation. An echocardiogram shows elevated pulmonary artery pressures. Amy is referred to a tertiary hospital PH clinic where she undergoes right-heart catheterisation and is diagnosed with PAH (Group 1 PH).

She begins targeted therapy with a phosphodiesterase type 5 inhibitor and an endothelin receptor antagonist. Her symptoms and pulmonary artery pressures improve dramatically. She is followed up every six months, and her condition remains stable for several years.

Learning points

- An intercurrent illness such as a respiratory infection, pulmonary embolism, ischaemic heart disease or comorbid heart failure can exacerbate underlying PH and trigger acute decompensation.
- Presyncope and syncope represent impaired cardiac reserve and indicate severe disease.
- Simple investigations may show abnormalities that alert the clinician to the possibility of PH. For example, chest radiography may show enlargement of the central pulmonary arteries, and an ECG may show right axis deviation, right ventricular hypertrophy or right ventricular strain. However, many patients do not have clearcut signs on examination or screening investigations.
- Targeted therapy to reduce pulmonary vascular resistance can result in significant clinical and physiological improvement in many patients with PAH.

unsuitable for surgery because of their pulmonary vasculature status, comorbidities or functional state.

Group 5. PH with unclear or multifactorial mechanisms

Group 5 PH includes conditions whose pathophysiology does not fit within Groups 1 to 4 PH. The mechanism driving abnormal pulmonary artery pressures in patients with Group 5 PH is often unclear. The most common cause of PH in this group is sarcoidosis.

Presentation

Clinical features of PH are nonspecific and include dyspnoea, fatigue, generalised weakness and, in later stages, chest pain, syncope and evidence of right heart failure. Given the nonspecific nature of these symptoms and the broad differential diagnosis, the diagnosis of PH is often overlooked, contributing to delayed management. Particularly in patients with PAH or Group 4 PH, opportunities are often missed to diagnose and treat disease at an early, potentially reversible stage before significant pulmonary vascular remodelling. A high index of suspicion is required as identifying patients early in the disease course and referring them to specialists with specific expertise in PH can improve functional and haemodynamic outcomes (see the case history in Box 2).[3,4]

Diagnosis

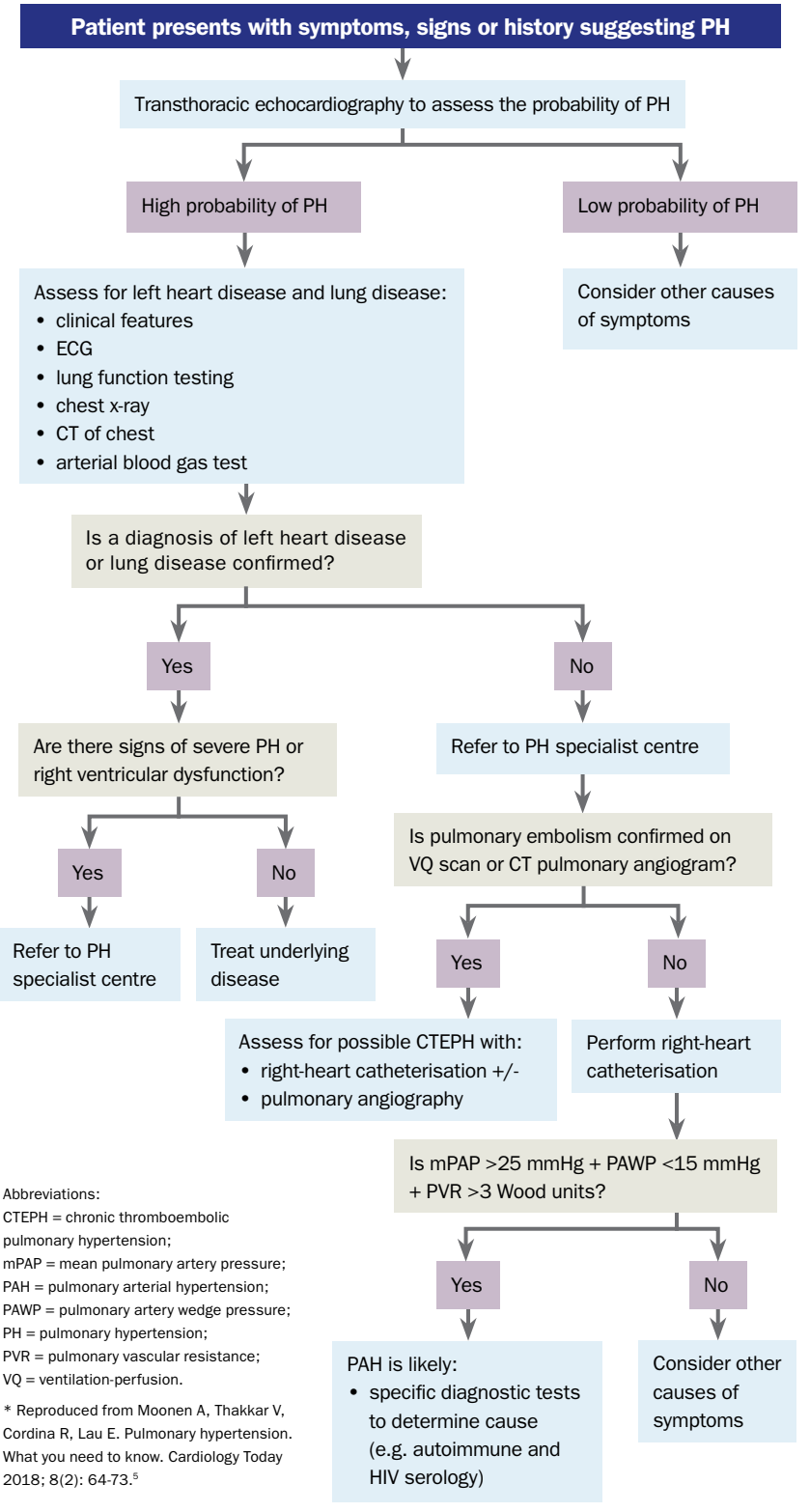
Diagnosis of PH requires a comprehensive set of investigations to confirm that haemodynamic criteria are met and to identify the aetiology and severity of the condition. Involvement of a multidisciplinary team with expertise in cardiology, respiratory medicine, imaging and connective tissue diseases is recommended. Given the complexity of managing patients with PH, referral to a clinic with expert medical, nursing, pharmacological and psychological support is also recommended.

A diagnostic algorithm that highlights the complexities involved in accurate diagnosis of PH and the need for early referral and multidisciplinary team involvement is shown in the Flowchart.[5]

Transthoracic echocardiography

Patients with suspected PH are recommended to undergo transthoracic echocardiography. If tricuspid regurgitation is present then the systolic pulmonary artery pressure can be estimated. Isolated or severe dilation of the right ventricle or atrium may

A suggested algorithm for the diagnostic work-up of patients with pulmonary hypertension[4]*



Abbreviations:
CTEPH = chronic thromboembolic pulmonary hypertension;
mPAP = mean pulmonary artery pressure;
PAH = pulmonary arterial hypertension;
PAWP = pulmonary artery wedge pressure;
PH = pulmonary hypertension;
PVR = pulmonary vascular resistance;
VQ = ventilation-perfusion.

* Reproduced from Moonen A, Thakkar V, Cordina R, Lau E. Pulmonary hypertension. What you need to know. Cardiology Today 2018; 8(2): 64-73.[5]

be a clue to PH if systolic pulmonary artery pressure cannot be estimated. GPs can help the supervising cardiologist by stating in the referral that PH is suspected. If possible, patients should be referred to an echocardiography service with experience investigating suspected PH. Stress echocardiography may provide additional information. However, occasionally PH is present and not detected by echocardiography.

In most cases, transthoracic echocardiography is performed on the basis of clinical suspicion of PH. However, transthoracic echocardiography screening for PH is recommended for asymptomatic patients in the following risk groups:

- patients with systemic sclerosis
- first-degree relatives of patients diagnosed with hereditary PAH
- patients with portal hypertension who are candidates for liver transplantation.

Right-heart catheterisation

Right-heart catheterisation is needed for a definitive diagnosis of PAH and clarification of the prognosis, as well as to quantify pulmonary artery pressure. Accurate measurement of cardiac output and pulmonary capillary wedge pressure are essential in evaluation of left heart causes of elevated pulmonary artery pressure. In addition, vasoreactivity challenge testing with a short-acting pulmonary vasodilator (e.g. inhaled nitric oxide) can identify a small subset of patients with PAH who have significant vasoreactivity and are best managed with high-dose calcium channel blockers.

Management

Targeted drug treatments are available for patients with PAH and some cases of chronic thromboembolic PH. The management of patients with other types of PH is discussed above (see specific PH groups).

The targeted treatments comprise pulmonary vasodilators that target the endothelin, nitric oxide or prostacyclin pathways, which are involved in pulmonary vasoconstriction and dilation (Figure).[5] These treatments fall into four major classes:

- phosphodiesterase type 5 inhibitors (e.g. sildenafil and tadalafil) – PAH

- soluble guanylate cyclase stimulators (e.g. riociguat) – PAH and Group 4 PH
- endothelin receptor antagonists (e.g. bosentan, macitentan and ambrisentan) – PAH
- prostacyclins and prostacyclin analogues (e.g. epoprostenol, iloprost and selexipag [the last is not PBS listed]) – PAH.

In addition, calcium channel blockers may be useful in the small proportion of patients with PAH who show an acute vasodilator response on vasoreactivity challenge testing.

Most patients with PAH are managed with combination therapy, particularly if they have moderate or severe disease. Combination therapy is ideally instituted upfront or in a rapid stepwise fashion. The complexities of these medications and their interactions and side effects mean that patients are best managed through designated PH prescribing centres.

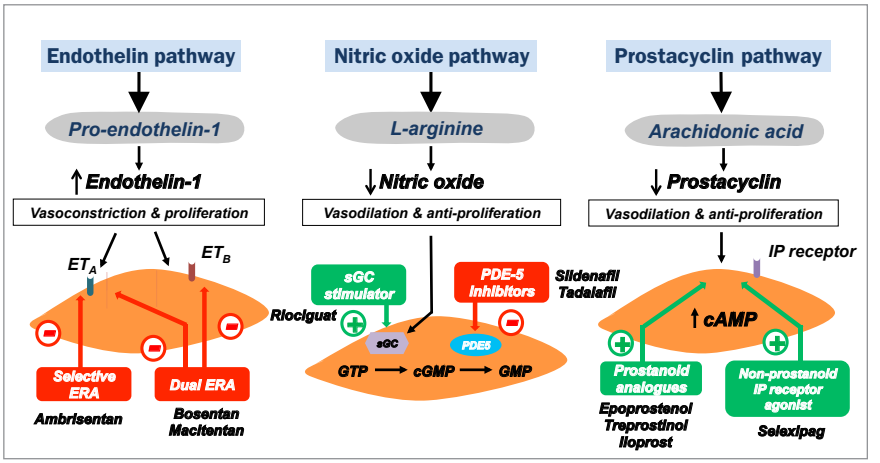


Figure. Molecular mechanisms of action of drugs used to treat pulmonary arterial hypertension (PAH). The key targets of PAH therapy are the endothelin, nitric oxide and prostacyclin pathways. In PAH, there is upregulation of vasoconstricting endothelin-1 and decreased production of vasodilatory nitric oxide and prostacyclin. The endothelin pathway can be blocked by selective or nonselective endothelin-1 receptor antagonists (ERA). The nitric oxide pathway can be enhanced by stimulation of soluble guanylate cyclase (sGC) or inhibition of phosphodiesterase type-5 (PDE-5). The prostacyclin pathway can be enhanced by prostanoid analogues or non-prostanoid IP receptor agonists.*

Abbreviations: cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GTP = guanosine triphosphate. * Reproduced from Moonen et al. Cardiology Today 2018; 8(2): 64-73.[4]

3. Case history: a man with dyspnoea and underlying cardiopulmonary disease

Case history

Richard, aged 68 years, has been attending a cardiology clinic annually since a myocardial infarction treated with a coronary stent six years earlier. He reports gradually worsening dyspnoea on exertion over several months to years and now struggles to walk around the block. He denies anginal symptoms or other chest pain, cough, sputum production, paroxysmal nocturnal dyspnoea, orthopnoea or wheeze.

Richard is an ex-smoker with a 30 pack-year history. He has a past diagnosis of mild-to-moderate chronic obstructive pulmonary disease (COPD), which has been stable for many years on tiotropium treatment. He has never seen a respiratory physician. He takes aspirin, rosuvastatin and telmisartan. His most recent echocardiogram was several years ago and showed a mildly reduced left ventricular ejection fraction of 50%. There was no comment on right heart function or pulmonary pressure. His symptoms are attributed to deconditioning and underlying COPD.

Learning points

- Although Richard has underlying cardiopulmonary disease, his new symptoms are out of proportion to the extent of disease and do not appear to be related either to an exacerbation of COPD or to worsening ischaemic heart disease. Decline in patients with otherwise stable cardiopulmonary conditions should alert the clinician to an alternative aetiology.
- Cardiologists and respiratory physicians not regularly treating patients with pulmonary hypertension (PH) may not specifically look for this condition if there is no pre-existing clinical history. Absence of PH reported in an echocardiogram does not exclude the condition.

Case history *continued*

Richard's breathlessness progresses and he presents to the emergency department with clinical signs of right heart failure. He is admitted and an echocardiogram reveals severe pulmonary hypertension with right ventricular dilatation. Right-heart catheterisation confirms the diagnosis of elevated pulmonary artery pressure and elevated pulmonary vascular resistance, with a normal pulmonary capillary wedge pressure. These features confirm a diagnosis of predominantly Group 1 PH – pulmonary arterial hypertension (PAH) – with a potential past contribution from Group 2 and Group 3 PH.

Richard is commenced on a phosphodiesterase type 5 inhibitor and an endothelin receptor antagonist. His symptoms decrease and a repeat echocardiogram shows improvement in right ventricular size and function. His results on the 6-minute walk test also improve.

Learning points

- Patients with risk factors for Group 2 and Group 3 PH can still have PAH if their pulmonary artery pressures are out of proportion to the severity of their cardiorespiratory disease and where significant left heart disease is excluded during right-heart catheterisation.
- Even patients with severe COPD typically develop only mild-to-moderate PH.
- Some patients with underlying cardiopulmonary disease and PAH may benefit from treatment with pulmonary vasodilator therapy in combination with optimisation of their underlying diseases. They should be managed in centres with experience in PH, preferably in the context of a well-conducted clinical trial.

4. Case history: a woman with hypertension and previous pulmonary embolism

Case history

Margaret, aged 64 years, presents to her GP with dyspnoea and lower limb swelling. She has a past history of hypertension and had a large, unprovoked pulmonary embolism five years ago. She was treated with warfarin for 18 months but then moved interstate and was lost to follow up. She is no longer taking anticoagulation treatment. The dyspnoea has worsened gradually over several months, and she reports atypical chest pain when climbing stairs.

Learning points

- Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism with an incidence of 0.5 to 4% after acute symptomatic pulmonary embolism.
- CTEPH should be considered in patients who present with persistent dyspnoea after a pulmonary embolism, even those who appear to have had adequate treatment for the embolism.
- Currently, there is no recommendation to screen all patients after a pulmonary embolism with CT pulmonary angiography or ventilation-perfusion scanning because of the low incidence of CTEPH. However, the failure to make a full functional recovery should prompt further evaluation.
- CTEPH affects the sexes equally, with a median age at diagnosis of 63 years.
- As with pulmonary arterial hypertension, there is typically a long delay between onset of symptoms and diagnosis, with high rates of misdiagnosis.

Case history *continued*

Margaret's GP refers her for a CT pulmonary angiogram, which shows chronic thrombus in the left main pulmonary artery and radiological evidence of pulmonary hypertension (PH). The GP refers her to a respiratory physician, who refers her on to a tertiary hospital PH clinic. Right-heart catheterisation and selective digital subtraction pulmonary angiography confirm severe PH secondary to CTEPH. Margaret undergoes surgical pulmonary endarterectomy. Her symptoms and pulmonary artery pressures improve dramatically.

Learning points

- Some patients with CTEPH may obtain complete cure with surgical management by pulmonary endarterectomy. Increasingly, balloon pulmonary angioplasty is being used in cases where surgery is not feasible.
- Early diagnosis is again important in identifying patients who may benefit from surgery and in instituting treatment at an early, potentially curable stage.
- Although CT pulmonary angiography often show features of CTEPH, ventilation-perfusion nuclear lung scanning is regarded as the best diagnostic test. Any persistent mismatched perfusion defect warrants further evaluation. Some patients can have persistent ventilation-perfusion inequality but have normal pulmonary pressures at rest when tested. This is referred to as chronic thromboembolic disease and can contribute to dyspnoea with activity. These patients should be monitored for the development of PH.
- Patients not suitable for pulmonary endarterectomy can be managed with targeted medical therapies. They require lifelong anticoagulation.
- Patients with CTEPH should be assessed and managed at dedicated CTEPH centres.

When and where to refer patients with PH

PH is rare and may coexist with more common causes of breathlessness (see the case history in Box 3). If there is evidence supporting the presence of a common cause of breathlessness then it is reasonable to treat this. A patient's failure to respond rapidly as expected to treatment should raise a red flag for the clinician, indicating a need for referral. If PH is suspected then prompt referral to a specialist with an interest in PH is crucial (see the case history in Box 4).

Local expertise often determines the referral pathway. Both cardiologists and respiratory physicians, along with some rheumatologists, have expertise in the assessment and management of patients with PH. A small number of designated centres are approved to prescribe PH medications. Expedited referral to one of these centres should facilitate final investigation, diagnosis and treatment with appropriate medications. This maximises the therapeutic benefits and can provide informed supportive care to patients and their carers.

Conclusion

With advances in management, PH has evolved into a treatable disease with improved survival. Early diagnosis and treatment are key to improving functional and haemodynamic outcomes. However, delayed diagnosis of PH remains common. Diagnosis and management of patients with PH is complex and best undertaken in designated PH clinics. **RMT**

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